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Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates

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Objectives: In the heterogeneous group of preterm and term neonates, gentamicin and tobramycin are mainly dosed according to empirical guidelines, after which therapeutic drug monitoring and subsequent dose adaptation are applied. In view of the variety of neonatal guidelines available, the purpose of this study was to evaluate target concentration attainment of these guidelines, and to propose a new model-based dosing guideline for these drugs in neonates.

Methods: Demographic characteristics of 1854 neonates (birth weight 390–5200 g, post-natal age 0–27 days) were extracted from earlier studies and sampled to obtain a test dataset of 5000 virtual patients. Monte Carlo simulations on the basis of validated models were undertaken to evaluate the attainment of target peak (5–12 mg/L) and trough (<0.5 mg/L) concentrations, and cumulative AUC, with the existing and proposed guidelines.

Results: Across the entire neonatal age and weight range, the Dutch National Formulary for Children, the British National Formulary for Children, Neofax and the Red Book resulted in adequate peak but elevated trough concentrations (63%–90% above target). The proposed dosing guideline (4.5 mg/kg gentamicin or 5.5 mg/kg tobramycin) with a dosing interval based on birth weight and post-natal age leads to adequate peak concentrations with only 33%–38% of the trough concentrations above target, and a constant AUC across weight and post-natal age.

Conclusions: The proposed neonatal dosing guideline for gentamicin and tobramycin results in improved attainment of target concentrations and should be prospectively evaluated in clinical studies to evaluate the efficacy and safety of this treatment.

Keywords: pharmacokinetics, NONMEM, aminoglycosides, therapeutic drug monitoring

Introduction

In the heterogeneous group of preterm and term neonates, gentamicin and tobramycin are mainly dosed according to empirically based dosing guidelines (see e.g.[1–4]), after which therapeutic drug monitoring (TDM) is applied and the dose potentially adapted. Whereas empirical dosing guidelines improve incrementally, a model-based dosing guideline can directly indicate the best treatment protocols for reaching target concentrations based on the available knowledge of the drug, therefore reducing the need for trial and error. While many dosing guidelines[1–4] and pharmacokinetic models exist for gentamicin and tobramycin, the models have only rarely been translated to clinical practice.[5,6]

Recently, a developmental model for the neonatal pharmacokinetics of amikacin was constructed and validated with external datasets that were not used in model building.[7] This model was subsequently extended to other renally cleared antibiotics such as netilmicin, vancomycin, tobramycin and gentamicin.[8]

This neonatal pharmacokinetic model was derived from data from 2437 neonates covering a wide range of birth weights (390–5200 g), which were used as predictors of antenatal maturation, and the whole range of post-natal ages, which were used as predictors of post-natal maturation.[7,8]

The goal of this study was to evaluate the performance of neonatal dosing guidelines for gentamicin and tobramycin of the Dutch National Formulary for Children (DNFc),[1] the British National Formulary for Children (BNFc),[2] Neofax[4] and the Red Book[3] in terms of adequate TDM concentrations, and to derive a model-based neonatal dosing guideline for these aminoglycosides. For this purpose, Monte Carlo simulations were performed using validated neonatal pharmacokinetic models of gentamicin and tobramycin to evaluate target peak and trough concentration attainment, and cumulative AUC over 1 week of treatment.[7,8]

Methods

Monte Carlo simulations ($n=5000$) were conducted for 1 week of treatment according to the dosing protocols outlined in the DNFc,[1] the BNFc,[2] Neofax[4] and the Red Book[3] (Tables S1 and S2, available as Supplementary data at *JAC* Online). The percentages of peak and trough concentrations above, at and below target range were computed. Peak concentrations of 5–12 mg/L[1,4] and trough concentrations <0.5 mg/L[2,4] were chosen as targets for the proposed dosing guideline and the proportion of patients reaching trough concentrations <1 mg/L was calculated. As aminoglycoside efficacy has been linked to exposure,[9] in addition, the cumulative AUC for 1 week of treatment was calculated according to the proposed dosing guideline to illustrate the uniformity of exposure across the patients.

For the simulations, a recently developed model for neonatal pharmacokinetics of gentamicin, tobramycin, amikacin, netilmicin and vancomycin was used.[8] In this model, clearance proved dependent on birth weight, representing antenatal maturation, on post-natal age, representing post-natal maturation, and on exposure to ibuprofen (decreasing clearance by 16%). Volume of distribution was dependent on current body weight.[8]

To be able to perform simulations for the entire preterm and term neonatal population, covariate data on birth weight, post-natal age, current weight and ibuprofen status were extracted from previously published studies.[5–7,10] This resulted in a combined dataset of 1854 patients with an average birth weight of 2100 g (range 390–5200 g, SD 1100 g), an average current body weight of 2100 g (range 390–5400 g, SD 1100 g) and an average post-natal age of 1.7 days (range 0–27 days, SD 2.7 days), with 206 (11%) of the patients receiving ibuprofen for closure of a persistent ductus arteriosus. From the collected dataset, 5000 individuals with a post-natal age <28 days were randomly sampled with replacement.

Simulations were performed with NONMEM 7.3 using GFortran 4.8.1.[11] Data manipulation was performed with R software version 3.1.1.[12]

Results

Table 1 shows that the existing dosing guidelines resulted in adequate peak concentrations in most of the cases (75%–88%), as did the proposed dosing guideline (82% and 91%). However, the four existing dosing guidelines also resulted in a high percentage of patients reaching trough concentrations above target, which is associated with renal and ototoxicity (Table 1). The proposed new dosing guideline (Table 2) not only reaches target trough concentrations in 62%–67% of the cases (Table 1), thereby comparing favourably with, for instance BNFc with percentages as low as 10%–15% (Figure 1), but also performs consistently across the observed covariate range of birth weight, current body weight and post-natal age, as shown in Figure 2. Approximately 95% of the predicted trough concentrations are <1 mg/L (Figure 2). Figure S1 shows that, even though the dosing protocol has been optimized for the attainment of peak and trough concentrations, it results in uniform 1 week cumulative AUC values for all subpopulations.

Discussion

In this work, the performance of commonly used gentamicin and tobramycin dosing guidelines for neonates was evaluated in terms of target peak and trough concentrations and AUC. Currently, neonates are dosed according to one of the available guidelines, after which TDM is performed and subsequent doses are adapted. As none of the evaluated guidelines performed well across the heterogeneous group of neonates varying in weight between 390 and 5200 g, an optimized dosing guideline was proposed, potentially leading to a reduced need for dose adaptation after TDM in this special population. It is emphasized

Table 1. Percentage of target peak and trough concentrations of gentamicin/tobramycin above, at and below target concentrations ($n=5000$)

Drug	Range	DNFc[1]	BNFc[2]	Red Book[3]	Neofax[4]	Proposed
Gentamicin	peak >12	6%	18%	13%	20%	9%
	peak 5–12	**82%**	**76%**	**78%**	**75%**	**82%**
	peak <5	12%	7%	9%	6%	9%
	trough ≤1	65%	35%	50%	50%	93%
	trough ≤0.5	**29%**	**10%**	**18%**	**17%**	**67%**
Tobramycin	peak >12	0%	1%	1%	1%	2%
	peak 5–12	**73%**	**85%**	**79%**	**88%**	**91%**
	peak <5	27%	14%	20%	11%	7%
	trough ≤1	74%	46%	63%	61%	90%
	trough ≤0.5	**37%**	**15%**	**26%**	**24%**	**62%**

Within-target concentrations are in bold.
The percentages do not always add up to 100% because of rounding rules.

Table 2. Proposed dosing intervals after a uniform dose of gentamicin (4.5 mg/kg) or tobramycin (5.5 mg/kg)

	bBW <1 kg (h)	bBW between 1 and 2 kg (h)	bBW >2 kg (h)
PNA ≤5 days	72	60	48
PNA between 6 and 10 days	60	48	36
PNA between 11 and 20 days	48	36	24
PNA >20 days	36	24	24

bBW, birth body weight; PNA, post-natal age.
The dosing interval should be increased by 12 h if ibuprofen is coadministered for closure of a persistent ductus arteriosus.

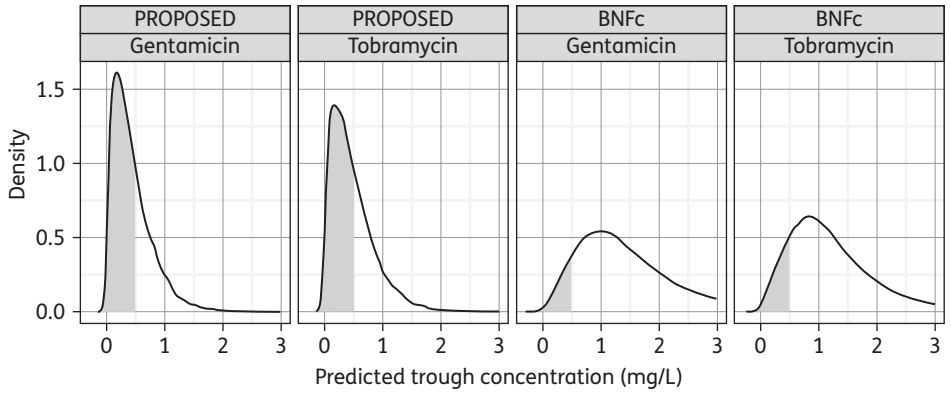

Figure 1. Performance of the proposed dosing guideline versus BNFc guideline during 1 week of treatment summarizing all trough concentrations during treatment. Grey areas represent concentrations under the target value of 0.5 mg/L.

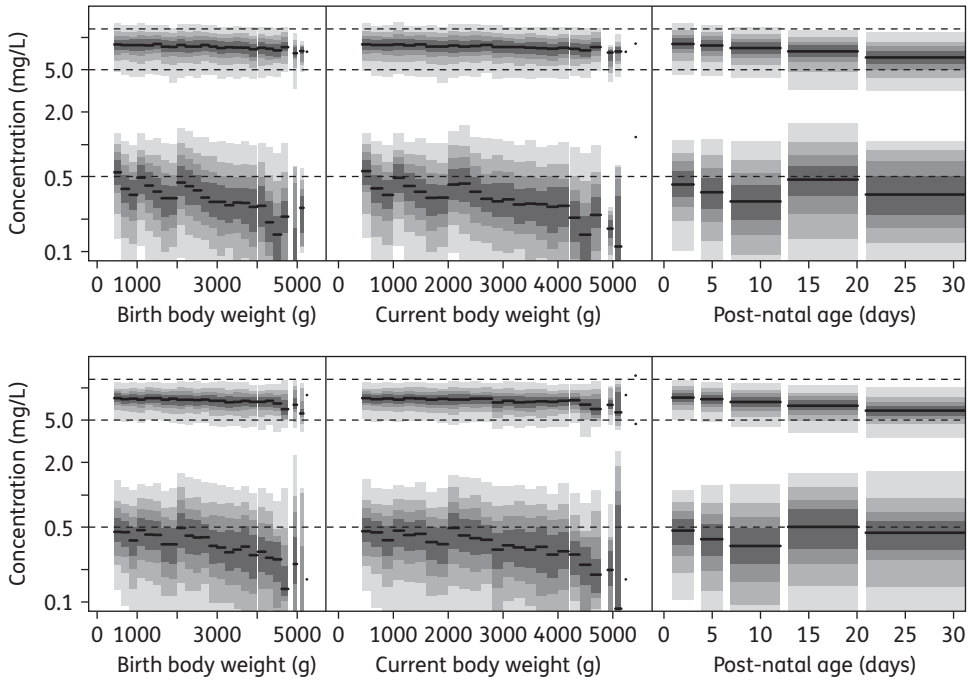

Figure 2. Performance of the proposed dosing guideline in terms of target peak and trough concentration attainment for gentamicin (top panels) and tobramycin (bottom panels) during 1 week of treatment, plotted against covariates birth weight, current body weight and post-natal age ($n = 5000$). The broken horizontal lines from top to bottom represent the upper and lower boundaries of target peak concentrations (5–12 mg/L) and the upper limit of the desired trough concentration (≤0.5 mg/L). The bold horizontal lines represent the median predicted concentrations of peak and trough concentrations. The grey layers represent the 90th, 70th, 50th and 30th percentiles of the predicted data.

that these dosing guidelines are proposed for neonates without renal insufficiency.

Even though there is an abundance of both dosing guidelines[1–4] and pharmacokinetic models, the available models have only rarely been translated to clinical practice.[5,6] An important finding of this study is the need for a different dose for gentamicin versus tobramycin (4.5 versus 5.5 mg/kg, respectively). This finding can be explained by the fact that tobramycin clearance and volume of distribution are higher than the respective pharmacokinetic parameters for gentamicin in neonates.[8] It has also been documented that gentamicin is more nephrotoxic than tobramycin.[13,14] We consider this a further indication that the two drugs require different doses.

In this work, dosing intervals of up to 72 h are proposed, whereas the highest dosing interval that we are aware of in an existing dosing guideline is 60 h.[15] There is a general historical trend in gentamicin and tobramycin dosing, moving from multiple-daily to once-daily dosing in adults[16,17] and towards even less frequent dosing in neonates.[5] Given this gradual shift, we propose that the most premature neonates need yet longer dosing intervals. Despite the longer dosing interval in the proposed dosing protocol, the predicted cumulative AUC is not decreased for the most premature neonates (Figure S1). Further, this cumulative AUC is not based on merely peak and trough samples; rather, it is based on a validated two-compartment pharmacokinetic model that is able to describe the full time course of drug concentrations.[7,8]

In conclusion, this work provides model-based dosing guidelines for gentamicin and tobramycin, which reflect state-of-the-art knowledge about the pharmacokinetics of these drugs and are also practical, minimizing the risk of dosing errors. Simplicity and ease of use (i.e. by restricting dosing intervals to multiples of 12 h) were considered a priority when devising the proposed dosing guideline. Simpler dosing guidelines are associated with fewer dosing errors than more complex ones.[18] Prospective validation in clinical studies of these dosing guidelines is needed to evaluate efficacy and safety of these model-based dosing guidelines.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 and Figure S1 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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